

Tuesday  
January 15, 1985

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## Part VIII

# Department of Health and Human Services

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Food and Drug Administration

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21 CFR Part 341

Cold, Cough Allergy, Bronchodilator, and  
Antiasthmatic Drug Products for Over-  
the-Counter Human Use; Tentative Final  
Monograph for OTC Antihistamine Drug  
Products

**DEPARTMENT OF HEALTH AND  
HUMAN SERVICES**
**Food and Drug Administration**
**21 CFR Part 341**
**[Docket No. 76N-052H]**
**Cold, Cough, Allergy, Bronchodilator,  
and Antiasthmatic Drug Products for  
Over-the-Counter Human Use;  
Tentative Final Monograph for OTC  
Antihistamine Drug Products**
**AGENCY:** Food and Drug Administration.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with antihistamine drug products and is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

**ADDRESS:** Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of September 9, 1976 (41 FR 38312) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, which was the advisory-review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18400), the agency advised that it had reopened the administrative record for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch. In response to the advance notice of proposed rulemaking, 12 manufacturers, 2 manufacturers' associations, 16 health care professionals, and 6 health care professional societies submitted comments on antihistamine drug products. Copies of the comments received are on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on antihistamine drug products is the fifth segment to be published. The first segment, on anticholinergic drug products and expectorant drug products, was published in the Federal Register of July 9, 1982 (47 FR 30002). The second

segment, on bronchodilator drug products, was published in the Federal Register of October 26, 1982 (47 FR 47520). The third segment, on antitussive drug products, was published in the Federal Register of October 19, 1983 (48 FR 46576). The fourth segment, on nasal decongestant drug products, is being published elsewhere in this issue of the Federal Register. A subsequent segment on combination drug products and general comments will be published in a future issue of the Federal Register.

The advance notice of proposed rulemaking, which was published in the Federal Register on September 9, 1976 (41 FR 38312), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule), FDA states for the first time its position on the establishment of a monograph for OTC antihistamine drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC antihistamine drug products.

This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on anticholinergic drug products and expectorant drug products that was published in the Federal Register of July 9, 1982 (47 FR 30002)) in Subpart A, by adding in § 341.3, new paragraph (d); in Subpart B, by adding new § 341.12; and in Subpart C, by adding new § 341.72, and by adding in § 341.90, new paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k). This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antihistamine drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler v. Kennedy*, 475 F. Supp. 838 (D.D.C. 1979).

(See the Federal Register of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug

products (published in the Federal Register of September 9, 1976 (41 FR 38312)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the Federal Register. The agency believes that within 12 months after the date of publication most manufacturers can show new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to

the call-for-data notice published in the Federal Register of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products recommended that doxylamine succinate be classified in Category I as an antihistamine at adult oral dosages of 7.5 to 12.5 milligrams (mg) every 4 to 6 hours, not to exceed 75 mg in 24 hours (see 41 FR 38419). However, since the Panel's report was published, controversy has arisen concerning whether or not there is an association of a prescription drug product containing doxylamine succinate with birth defects. This drug product is prescribed as an antinauseant for use during pregnancy. In 1982, Eskenazi and Bracken (Ref. 1) reported the results of a case control study of 1747 women, which suggests that a child born to a mother who used the doxylamine containing product was at an approximately four fold increased risk for developing pyloric stenosis. The Boston Collaborative Drug Surveillance Program recently reported to the agency preliminary results of a cohort study that also found an association between exposure to a product containing doxylamine succinate during pregnancy and the occurrence of pyloric stenosis in infants. The reported increase in risk was 2.7 fold, a finding consistent with the Eskenazi and Bracken study. Preliminary results from this study suggest risk increasing with increasing numbers of prescriptions. These reports, however, do not establish that the association is causal. Other factors, in particular, the nausea and vomiting, may account for the observed association. Mitchell et al. (Ref. 2) recently presented the findings of a case-control study conducted by the Drug Epidemiology Unit of Boston University. This study, representing by far the largest available data base, compared the use of a product containing doxylamine succinate among the mothers of 325 infants with pyloric stenosis to its use in mothers of 3,153 infants with other malformations. No association between the use of a product containing doxylamine succinate during pregnancy and the development of pyloric stenosis was found. In addition, the agency has examined Medicaid data to determine whether in this data base there is an association between the use of a doxylamine succinate containing drug

product by women during pregnancy and the occurrence of pyloric stenosis in infants (Ref. 3). Based on an analysis of these data, the agency has concluded that the Medicaid data do not support such an association.

The agency is aware that at this time the scientific and medical communities are actively discussing and debating whether or not doxylamine succinate, in fact, plays a causal role in reported birth defects. This subject has been discussed and debated without resolution at several scientific meetings such as the Teratology Society meeting and the Society for Epidemiologic Research meeting that were held in June 1984. The possible association of doxylamine succinate with birth defects continues to be disputed.

The time necessary to complete a full review and evaluation of the new studies concerning the use of a product containing doxylamine succinate and birth defects could result in a considerable delay in the publication of the tentative final monograph for OTC antihistamine drug products. Accordingly, the agency has decided to remove all discussion of the safety and effectiveness of doxylamine succinate from this document.

The agency intends to review and evaluate the new data and information concerning the relationship between doxylamine succinate and birth defects that is currently being generated in as expeditious a manner as possible. Based on its review and evaluation of the data and information, the agency will publish a separate document in the *Federal Register* addressing the status of this ingredient.

At this time, drug products containing doxylamine succinate as an OTC antihistamine will remain in the marketplace with the warning required for all OTC drug products, as follows: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

#### References

- (1) Eskenazi, B., and M. Bracken, "Bendectin (Debenox) as a Risk Factor for Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 144:919-924, 1982.
- (2) Mitchell, A. A., et al., "Birth Defects in Relation to Bendectin Use in Pregnancy II. Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 147:737-742, 1983.
- (3) Rosa, F.W., draft of unpublished study, OTC volume 04HTEM, Docket No. 76N-052H, Dockets Management Branch.

#### I. The Agency's Tentative Conclusions on the Comments

##### A. General Comments on Antihistamine Drug Products

1. One comment stated that the Panel gave certain antihistamines (i.e., diphenhydramine, methapyrilene, phenindamine, pheniramine, promethazine, pyrilamine, and thonzylamine) Category I status on the basis of low-quality evidence. The comment stated that the Panel recognized that there were no controlled clinical trials for these drugs, that chronic toxicity studies in animals had not been performed, and that there was no evidence that systematic literature searches were conducted or that FDA adverse reaction files were studied. The comment concluded that these drugs have been adjudged "safe" on the basis of superficial information. The comment contended that controlled clinical trials are required for general recognition of safety and effectiveness. The comment recommended that a complete new review of cough and cold ingredients be conducted by FDA and that FDA impose an immediate ban of all ingredients that are not proven safe and effective by scientific studies equivalent to those required for prescription drugs.

In determining that certain antihistamines should be generally recognized as safe and effective for OTC use, the Panel followed applicable regulations relating to the OTC drug review. The regulations, at 21 CFR 330.10(a)(4)(i), state: "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."

The Panel's conclusions as to the safety of the aforementioned antihistamine drugs were arrived at in accordance with the above regulation. For the determination of safety, the Panel reviewed published and unpublished studies, Poison Control Center statistics, FDA adverse reaction reports, and other data in the literature, and it used clinical and marketing experience to corroborate these data.

Subsequent to the Panel's determinations, new data were developed concerning some of these ingredients. On the basis of these data, the agency has taken appropriate regulatory action and in this tentative final monograph is making necessary

changes to the Panel's recommendation. For example, the Panel recommended classification of methapyrilene hydrochloride and methapyrilene fumarate in Category I as antihistamines. Subsequent to this recommendation, a National Cancer Institute (NCI) study, not available to the Panel, provided data from which the agency concluded that methapyrilene is a potent carcinogen in animals and must be considered a potential carcinogen in man. These data are on file in the Dockets Management Branch (address above) under Docket No. 75N-0244 and have been published (Ref. 1).

In June 1979, the agency initiated a recall of all oral and topical products containing methapyrilene. Manufacturers have voluntarily recalled all methapyrilene-containing products from the market, and FDA has withdrawn all NDAs for products containing methapyrilene. Products containing methapyrilene are considered misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)). The agency has therefore placed methapyrilene fumarate and methapyrilene hydrochloride in Category II in this document.

The Panel recommended a Category I classification for promethazine hydrochloride. However, the agency has concerns regarding the safe use of promethazine hydrochloride as an OTC antihistamine and has determined that although promethazine hydrochloride has been widely used as a prescription drug product with a relatively low incidence of serious adverse reactions, at this time general recognition of the safety of this ingredient for long-term use as an OTC antihistamine has not been adequately established. (See comment 9 below.) Therefore, the agency is proposing that promethazine hydrochloride be Category III at this time as an OTC antihistamine.

For the determination of effectiveness, the agency agrees that the studies on which the Panel based its conclusions concerning diphenhydramine hydrochloride, phenindamine tartrate, pyrilamine maleate, and thonzylamine hydrochloride were not well-controlled. However, the Panel reviewed published studies, as cited in its report, and used clinical and marketing experience to corroborate these studies. The agency concludes that the evidence in these studies and the Panel's expertise in evaluating the clinical and marketing experience are sufficient to establish

general recognition of effectiveness of these ingredients as antihistamines.

The agency has reviewed the Panel's recommendations and all of the supporting data and concludes that there is a sufficient basis to determine that brompheniramine maleate, chlorpheniramine maleate, diphenhydramine hydrochloride, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, and thonzylamine hydrochloride are generally recognized as safe and effective when used as ingredients in antihistamine drug products intended for OTC use.

#### Reference

(1) Lijinsky, W., M. D. Reuber, and B. N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817-819, 1980.

2. Several comments pointed out that the table of symptoms and pharmacological groups in part II, paragraph B. of the Panel's report (41 FR 38320) omitted antihistamines as a pharmacological group for treating runny nose. The comments stated that both the report and the Panel's recommended monograph contain "running nose" as a Category I claim for antihistamines. Several of the comments also criticized the Panel's omission from the table, the report, and the monograph of antihistamines as a pharmacological group for treating "sinus congestion." These comments argued that because "congestion" is a symptom of allergic rhinitis, and the Panel has placed antihistamines in Category I for the alleviation of the symptoms of allergic rhinitis, "sinus congestion" should be included as a symptom to be treated with antihistamines.

The agency agrees the antihistamines were inadvertently omitted from the table of symptoms and pharmacological groups as a treatment for runny nose. Runny nose as may occur in allergic rhinitis is listed as a Category I claim for antihistamines in the Panel's report and in § 341.72(a) (1), (2), and (6) of its recommended monograph. Therefore, the table of symptoms and pharmacological groups in part II, paragraph B. is amended by the publication of this document.

The agency does not agree that antihistamines should be included in the table, report, or recommended monograph for the treatment of "sinus congestion." The Panel recommended antihistamines only for the treatment of specific symptoms, i.e., runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes associated with allergic rhinitis, and did not

recommended antihistamines for the alleviation of all symptoms associated with allergic rhinitis, as stated by the comment. Sinus congestion may result in impaired sinus drainage due to nasal obstruction caused by allergic rhinitis or the "common cold." The Panel reviewed studies that measured the effects of antihistamines or nasal obstructions (Refs. 1, 2, and 3). These studies demonstrated that antihistamines did not reduce nasal obstruction and therefore did not aid in sinus drainage. To the contrary, the studies indicated that antihistamines may sometimes further aggravate nasal obstruction (Refs. 2 and 3). For that reason, the Panel placed antihistamines in Category 11 for claims for the relief of symptoms such as nasal obstructions, nasal stuffiness, etc. The Comments did not provide any data that demonstrate that antihistamines are effective in the treatment of "sinus congestion." The agency concurs in the Panel's Category II classification.

#### References

- (1) OTC Volume 040306.
- (2) OTC Volume 040114.
- (3) OTC Volume 040123.

3. One comment stated that two antihistamines should not be taken simultaneously and recommended that the labeling should be clear on this matter. The comment did not further elaborate on its statement.

The comment did not provide any information or examples. It is not clear whether there was concern about the simultaneous ingestion of two drug products each containing antihistamines ingredients that are specifically labeled as "antihistamines" or the simultaneous ingestion of two different drug products both containing antihistamines ingredients but for different use, e.g., one product labeled for "nighttime sleep-aid use" with no labeling as an antihistamine and another product labeled for "antihistamines use."

The agency recognizes that such products are currently available in the OTC drug marketplace but is unaware of any information that would raise health concerns. It is unlikely that a consumer would concurrently take two different OTC drug products both containing antihistamines. The proposed labeling for antihistamines in this tentative final monograph specifically requires that the product's principal intended use, i.e., "antihistamines," be stated in the labeling. By reading the labels, a consumer is made aware that different drug products contain antihistamine intended to treat the same symptoms. Therefore it is unlikely that

two such products would be taken simultaneously.

The agency recognizes that at least one antihistamine ingredient, diphenhydramine hydrochloride, because of its numerous pharmacologic properties, is marketed as an "antihistamines," "antitussive," and "nighttime sleep-aid" drug product. A consumer could simultaneously ingest two such products to alleviate concurrent symptoms. However, the agency is unaware of any information that this does occur. In addition, the agency is unaware of any data demonstrating that the simultaneous ingestion of two antihistamines labeled for different uses would result in a significant safety problem.

Therefore, the agency believes that the proposed labeling for antihistamines drug products in this tentative final monograph is adequate and that at this time there is no justification for expanding the labeling to include specific warnings regarding the simultaneous ingestion of two antihistamines. The agency invites specific comments on this issue.

4. Several comments requested that antihistamines, such as chlorpheniramine maleate, be allowed to make claims for the treatment of symptoms of the common cold. Symptoms for which Category I labeling claims were requested included the relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes when associated with the common cold. Two comments provided new data describing the results of clinical studies in which chlorpheniramine maleate was evaluated for treating symptoms of the common cold (Ref. 1). Another comment stated that there was little evidence to substantiate the usefulness of antihistamines for treating symptoms of the common cold and that, in fact, there are studies that demonstrate a lack of effectiveness for the use of antihistamines in treating symptoms of the common cold. The comment did not identify these studies.

The agency has reviewed the new data submitted in support of the use of chlorpheniramine maleate in treating the symptoms of the common cold enumerated above. The data submitted included independently conducted, multicenter, double-blind studies in which chlorpheniramine maleate was compared with a placebo in patients with the common cold over a 7-day period. In design and overall methodology, these studies follow the guidelines recommended by the Panel for studying antihistamines in the treatment of symptoms associated with

the common cold. An additional study conducted by a single investigator included 196 patients with the common cold who were followed for a 2-day period. This study was similar to the multicentered studies except for the length of time the patients were studied. The studies provide evidence that chlorpheniramine is significantly more effective than a placebo in alleviating the symptoms of runny nose and sneezing associated with the common cold. However, the data do not provide statistical evidence to show that chlorpheniramine is effective in relieving itching of the nose or throat, or itchy, watery eyes associated with the common cold. The agency has, therefore, concluded that chlorpheniramine is effective in treating runny nose and sneezing associated with the common cold. Because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine allow Category I status for these claims to be extended to all Category I antihistamine active ingredients. Accordingly, an indication for the temporary relief of runny nose and sneezing associated with the common cold has been added to proposed § 341.72(b) of this tentative final monograph.

#### Reference

(1) Comment Nos. SUP004 and SUP005, Docket No. 76N-0052, Dockets Management Branch.

5. One comment recommended that, in view of the reported toxicity of brompheniramine maleate and chlorpheniramine maleate, the quantity of these antihistamines contained in OTC packages should be limited. For example, the comment recommended limiting brompheniramine and chlorpheniramine products to 24 foil-wrapped tablets for the 4-mg strength tablets and to 12 tablets for the 8- and 12-mg strength tablets. The comment also recommended that containers of larger quantities of these antihistamines have child-resistant closures. The comment did not provide any data to support its recommendations.

FDA has established quantity limitations for certain OTC drugs in order to limit the possibility of accidental poisoning of children. See, for example, 21 CFR 201.308 (ipecac syrup) and 21 CFR 201.314 (children's aspirin). The Consumer Product Safety Commission (CPSC), however, has the authority to require child resistant closures for OTC drug containers. FDA is aware that CPSC has reviewed the available data on antihistamines to determine if child-resistant closures are

warranted for OTC drug products containing these ingredients. CPSC has published a final rule that drug products containing more than 75 mg diphenhydramine hydrochloride in a single package and in a dosage form intended for oral administration be required to have child-resistant packaging. (See CPSC Requirements for Child-Resistant Packaging: Diphenhydramine Hydrochloride published in the Federal Register on February 15, 1984; 48 FR 5337.) CPSC found that serious toxic effects can be produced with doses of diphenhydramine hydrochloride as low as 100 mg.

CPSC reviewed the toxicity of antihistamines other than diphenhydramine. However, it did not propose that any antihistamine other than diphenhydramine be required to be packaged with child-resistant closures. Because of the lack of significant toxicity data for antihistamines other than diphenhydramine, CPSC concluded that child-resistant closures were not necessary for these drugs, regardless of the amount of drug contained in each package.

The comment did not submit any data demonstrating a need to limit the package size of non-diphenhydramine antihistamine drug products. Moreover, FDA does not have other data or information showing that limiting the package size for these antihistamines is necessary. In the case of diphenhydramine, CPSC is requiring that child-resistant closures be used for packages of drug products containing greater than 75 mg diphenhydramine. If the agency proposed limiting the package size of such drug products to 75 mg diphenhydramine or less, each package would contain only six children's doses of 12.5 mg or one and one-half adult doses of 50 mg. Limiting the package size to such low numbers of dosages would be impractical. The agency believes that CPSC's requirement for child-resistant closures for drug products containing diphenhydramine provides a sufficient safeguard against accidental overdose in children, and that package size limitations are therefore unnecessary for such drug products.

#### *B. Comments on Switching Prescription Antihistamine Active Ingredients to OTC Status*

6. Several comments agreed and others disagreed with the Panel's recommendation to allow the OTC marketing of certain antihistamines which were previously available only by prescription or at higher dosage levels than those currently permitted for OTC

use. The comments which disagreed with the Panel unanimously recommended that those antihistamines which were previously available by prescription only, i.e., promethazine hydrochloride, diphenhydramine hydrochloride, brompheniramine maleate, chlorpheniramine maleate at a dosage of 4 mg, should remain prescription products. In general, the comments expressed opinions, without supporting data, that the benefits obtained from allowing these antihistamines to become available OTC would not outweigh the risks to which consumers would be exposed. Among the risks mentioned were (1) toxic effects from overdosage, (2) varying degrees of drowsiness and different adverse reactions in different patients, (3) a potential for becoming dependent on the sedative effect of antihistamines, (4) the development of a tolerance to antihistamines, and (5) confusion among consumers from too many antihistamines on the market. The comments also expressed concern that asthmatics with severe bronchitis would suffer from a thickening of secretions due to the anticholinergic effect of antihistamines.

In the preamble to the Panel's report at 41 FR 38313, the agency disagreed with the Panel's classification of diphenhydramine hydrochloride as a Category I antihistamine. The agency's objection to the Panel's recommendation to place these ingredients in Category I was based on the degree of drowsiness produced as a side effect. Subsequently, in a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an OTC antitussive drug product, published in the Federal Register of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling and packages the drug in child-resistant containers." The requirement of child-resistant closures has been addressed in comment 5 above. The agency, therefore, is proposing in this tentative final monograph that diphenhydramine hydrochloride at an adult dosage of 25 to 50 mg and doxylamine succinate at an adult dosage of 7.5 to 12.5 mg every 4 to 6 hours be Category I as OTC antihistamine drug products. (See comments 8 and 15 below.)

The agency disagrees with a comment that contended that higher doses of chlorpheniramine maleate should not be allowed OTC. Chlorpheniramine maleate has been available by prescription at the 4-mg dosage level

and OTC at the 2-mg and the 4-mg dosage levels; however, data reviewed by the Panel shows that chlorpheniramine maleate at a dosage of 4 mg every 4 to 6 hours is the minimum effective dosage for adults. Therefore, the agency is proposing that chlorpheniramine maleate be available OTC at the 4-mg dosage. The warning statements proposed in § 341.72 of this tentative final monograph will advise consumers of the appropriate use of antihistamines and of the risks associated with them. (See comment 12 below.)

The agency agrees with the Panel's classification of brompheniramine maleate and is proposing that this ingredient be Category I.

Issues regarding the safety of promethazine hydrochloride have not yet been resolved. The agency is proposing a Category III classification of this ingredient at this time. (See comment 9 below.)

7. One comment contended that the antihistamine dexchlorpheniramine maleate should be made available OTC. The comment explained that chlorpheniramine maleate, which the Panel classified as a Category I antihistamine, is a mixture of dextro- and levo-optical forms in which most of the activity of the antihistamine results from the dextro-optical form. The comment pointed out that dexchlorpheniramine maleate is composed of the dextro-optical form. The comment argued that a small dose of the more active dexchlorpheniramine would give the same effectiveness as a larger dose of chlorpheniramine and would, therefore, be safer because patients would be exposed to a small amount of active ingredient. The comment cited "The United States Dispensary" (Ref. 1) in support of its argument, as follows: "... it would appear that administration of the dextro isomer in half the dose of the racemic compound would provide practically the same antihistaminic activity as the latter (i.e., chlorpheniramine) and but half of its toxic effects; the expectation has been confirmed clinically." The comment recommended that the agency classify dexchlorpheniramine maleate as a Category I antihistamine in doses of 2, 4, and 6 mg.

Dexchlorpheniramine maleate is currently marketed under an approved abbreviated new drug application (ANDA) as a prescription drug at a dose of 2 mg every 4 to 6 hours for adults, a dose of 1 mg every 4 to 6 hours for children 6 to under 12 years of age, and a dose of 0.5 mg every 4 to 6 hours for children 2 to under 6 years of age (Refs. 2 and 3). Chlorpheniramine maleate is

currently marketed as an OTC antihistamine drug, and the agency is proposing to place chlorpheniramine maleate in Category I at a dose of 4 mg every 4 to 6 hours for adults and a dose of 2 mg every 4 to 6 hours for children 6 to under 12 years of age. (See comment 12 below.)

An in vitro and an in vivo study of dexchlorpheniramine maleate, chlorpheniramine maleate (racemic mixture), and the levo-optical form of chlorpheniramine maleate in guinea pigs and dogs has demonstrated that the dextro-optical form (dexchlorpheniramine maleate) of chlorpheniramine maleate is the active moiety in the racemic mixture (Ref. 4). The data from this study demonstrate that dexchlorpheniramine maleate has approximately twice the antihistaminic activity of chlorpheniramine maleate (racemic mixture). Therefore, the appropriate OTC dosages for dexchlorpheniramine maleate are half the proposed dosages for chlorpheniramine maleate.

A review of FDA adverse reaction reports since 1976 (Ref. 5) indicates that only one adverse reaction (a patient fainting) has been reported in cases where dexchlorpheniramine maleate was the only drug given.

Based on the safe and effective use of dexchlorpheniramine maleate under an approved ANDA, the safe and effective use of chlorpheniramine maleate for many years as an OTC antihistamine, and a review of FDA adverse reaction reports, the agency believes that dexchlorpheniramine maleate can be generally recognized as safe and effective for OTC use. The agency is therefore proposing that dexchlorpheniramine maleate be classified as Category I as an OTC antihistamine at a dose of 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, for adults and a dose of 1 mg every 4 to 6 hours, not to exceed 6 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes a dose of 0.5 mg every 4 to 6 hours, not to exceed 3 mg in 24 hours, for children 2 to under 6 years of age under professional labeling in the tentative final monograph. The labeling warnings are identical to those being proposed for chlorpheniramine maleate.

Only timed-release dosage forms are currently approved for adult doses greater than 2 mg every 4 to 6 hours. An approved NDA is required for such products. (See comment 13 below.) Therefore, dosages of 4 to 6 mg will not be included in this tentative final monograph.

Although the agency is proposing in this tentative final monograph to switch

dexchlorpheniramine maleate to OTC use from its present status as a prescription drug, OTC marketing may not begin at this time. In the Federal Register of June 3, 1983 (48 FR 24925), FDA explained the enforcement policy for drugs that were originally on prescription status but which were being proposed for OTC marketing under the OTC drug review. As noted there, 21 CFR 330.13 permits OTC marketing of a drug previously limited to prescription use prior to publication of a final monograph provided that certain conditions are met. To qualify for such treatment, the drug must, at a minimum, have been considered by an OTC drug advisory review panel and either recommended for OTC marketing by the panel or subsequently determined by FDA to be suitable for OTC marketing. Dexchlorpheniramine maleate was not considered by a panel and, therefore, does not qualify for early OTC marketing under the terms of the enforcement policy set out in § 330.13. Moreover, FDA believes that the drug is not appropriate for OTC marketing at this time. FDA believes that public comments submitted in response to the proposed switch in status should be evaluated before OTC marketing is begun. Accordingly, until such comments are reviewed, dexchlorpheniramine maleate remains a prescription drug subject to the terms and conditions specified in its approved ANDA.

#### References

- (1) Osol, A., R. Pratt, and A.R. Gennaro, "The United States Dispensary," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 302, 1973.
- (2) Letter from M. Seife, FDA, to Schering Corporation, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (3) Copy of FDA-approved labeling from ANDA 86-835, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (4) Roth, F. E., and W. M. Govier, "Comparative Pharmacology of Chlorpheniramine (Chlor-trimeton) and Its Optical Isomers," *Journal of Pharmacology and Experimental Therapeutics*, 124:347-349, 1958.
- (5) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1976-1982, included in OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

8. A number of comments discussed the Panel's recommendation to allow diphenhydramine hydrochloride to be marketed OTC for use as an antihistamine. The comments varied from complete disagreement with the Panel's recommendation to suggestions that the agency place limitations on the

strength of the tablets and/or the size of the packages and that child-resistant closures be required for all OTC products containing this ingredient. One comment suggested that diphenhydramine hydrochloride be available OTC only after consultation with a pharmacist or "prescriber." All of the comments were concerned about diphenhydramine hydrochloride's pronounced tendency for causing drowsiness.

In the preamble to the Panel's report at 41 FR 38313, the agency dissented from the Panel's Category I classification of diphenhydramine hydrochloride as an OTC antihistamine ingredient. It was pointed out that at that time no product containing diphenhydramine hydrochloride was marketed OTC as an antihistamine at any dosage level. In the preamble to the Panel's report, the agency also deferred a decision on the Panel's recommendation to place diphenhydramine hydrochloride in Category I as an antitussive ingredient until the agency made a decision concerning a pending supplemental NDA for OTC status of diphenhydramine hydrochloride as an antitussive. Subsequently, in a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an antitussive drug product published in the *Federal Register* of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling and packages the drug in child-resistant containers." Diphenhydramine presently is marketed OTC as an antitussive under an approved supplemental NDA.

The agency believes that the proposed warning in this tentative final monograph that reads, "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery" and the warning for products labeled for children under 12 years of age that reads "May cause marked drowsiness" are adequate to allow OTC marketing of diphenhydramine hydrochloride. These warnings are similar to those required under the approved supplemental NDA for the antitussive drug product containing diphenhydramine.

The agency, therefore, is proposing diphenhydramine hydrochloride as Category I in this tentative final monograph for use as an OTC antihistamine at an adult dosage of 25 to

50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours, and for children 6 to 12 years of age at a dosage of 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours.

9. Many comments were opposed to the Panel's classification of promethazine hydrochloride as a Category I antihistamine for relieving the symptoms of allergic rhinitis. These comments agreed with the agency's decision (as stated in the preamble of the Panel's advance notice of proposed rulemaking) to limit promethazine hydrochloride to its present status as a prescription drug. The comments asserted that promethazine should not be available on an OTC basis because of (1) its adverse side effects (especially sedation and blood dyscrasias), (2) the potential for abuse and overdosage, (3) the risk in children, and (4) the possibility of increased development of promethazine-induced dyskinesias. The comments concluded that the risk of adverse effects from the OTC availability of promethazine hydrochloride is not justified in the absence of an offsetting benefit in the form of therapeutic superiority in comparison with antihistamine ingredients already marketed OTC.

Only one comment (a reply comment) agreed with the Panel's Category I classification, contending that promethazine has an outstanding safety record based on its long history of use, that there was no basis for implicating promethazine hydrochloride as the cause for blood dyscrasias, and that promethazine hydrochloride cannot be distinguished from other OTC antihistamines in terms of its sedative and other adverse effects on the central nervous system.

After reviewing these comments, the Center for Drugs and Biologics (CDB) expressed its concerns regarding the effect of promethazine hydrochloride on the central nervous system in a feedback letter to a manufacturer (Ref. 1). Based on an incidence of 1 in 2,468 (0.04 percent) of extrapyramidal syndrome associated with the use of promethazine hydrochloride that was cited by the Panel (41 FR 38390) and a report of four cases of choreoathetosis that were related to the use of promethazine at dosages comparable to those recommended by the Panel (Ref. 2), the CDB questioned whether a drug with the side effect of choreoathetosis and a known incidence of extrapyramidal side effects has an acceptable benefit-to-risk ratio for OTC use. The agency had previously stated in the preamble of the Panel's report (41 FR 38312) that children seem particularly

liable to develop adverse central nervous system reactions, such as extrapyramidal disturbances from the use of promethazine. CDB added that it does not consider the rare drug-related cases of blood dyscrasias an issue that would preclude OTC use of this ingredient inasmuch as other OTC antihistamines also can be associated with such reactions, but because of its other concerns was proposing that promethazine hydrochloride be placed in Category III.

In response to this letter, the manufacturer petitioned the agency to reopen the administrative record for the OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products rulemaking to include new data and information regarding the safety of promethazine hydrochloride (Refs. 3 and 4). The new data and information submitted by the manufacturer clarify the data regarding the incidence of extrapyramidal effects associated with the use of promethazine in both adults and children and point out errors in the data cited by CDB regarding the association between the use of promethazine and the occurrence of choreoathetosis. The agency has included these data and information in the administrative record for this rulemaking in reaching its decision on the status of promethazine in this tentative final monograph (Ref. 5).

The manufacturer noted that the CDB's information on the 0.04 percent incidence rate of extrapyramidal syndrome was based on only one case in 2,468 patients, as cited by the Panel at 41 FR 38390. The manufacturer stated that its review of the single case report disclosed that it involved the injectable dosage form of promethazine and not the oral dosage form. The agency has confirmed that this is correct. The 0.04 percent incidence rate was derived from the Panel's review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program (BCDSP) and the University of Florida Adverse Reaction Study. The manufacturer included in its petition a statement from Jick, a recognized epidemiologist of the BCDSP, that the one case cited by the Panel is the only United States case of extrapyramidal syndrome reported through the BCDSP program (Ref. 4). Jick added that the data in BCDSP were updated through the end of 1981, and four additional cases of extrapyramidal symptoms, all of which were from Western Europe, were identified. Of the four cases, three involved injectable promethazine in relatively high doses, and only one case involved a patient who received oral promethazine. Jick

stated that the patients were elderly, had chronic pulmonary problems and other serious disorders, and received other medications that are likely to have influenced what occurred. Jick concluded that the data do not indicate that promethazine at the suggested OTC oral dosages would present any important risk of the occurrence of extrapyramidal symptoms.

The manufacturer added that the only other reference cited in the agency's letter that describes cases of extrapyramidal effects associated with promethazine was the ADR Highlights (Ref. 2). Fourteen cases are described, of which four purportedly involved promethazine. The manufacturer stated that the ADR Highlights omitted information on the route of administration of the drug in addition to containing other errors on the drugs involved and the doses administered.

The agency acknowledges that inaccuracies existed in the data base and that correction of these errors leads FDA to conclude that the possibility of choreoathetosis occurring with OTC oral doses of promethazine is unlikely. This conclusion is supported by a review of FDA adverse reaction data for the period 1970-1981 and a review of the published literature. These sources reveal only a few cases of extrapyramidal effects possibly associated with dosages of promethazine that would be available OTC. Also, based on the above data, there is no evidence to indicate that these effects would be more likely to occur in children. Based upon the available data, the agency's concerns regarding the occurrence of extrapyramidal effects and choreoathetosis and the concern that children seem particularly liable to develop adverse central nervous system reactions to promethazine have been adequately addressed. Thus, these are no longer issues that would preclude use of this ingredient at proposed OTC oral dosages.

The agency has also reviewed additional information on promethazine obtained from the National Prescription Audit (NPA) and the National Disease and Therapeutic Index (NDTI) data systems (Ref. 6). The data show that promethazine hydrochloride has been widely used as a prescription drug product, primarily in combination with other active ingredients, with a relatively low incidence of serious adverse reactions. The agency has further concerns regarding the safe use of this ingredient solely as an OTC antihistamine drug product, particularly for extended periods of time as for

allergy treatment. Promethazine hydrochloride is a phenothiazine, and long-term phenothiazine therapy has been associated with the occurrence of tardive dyskinesia (Ref. 7), a serious central nervous system syndrome that may persist indefinitely after discontinuation of the medication. Some of the comments also expressed concern about the possibility of increased development of promethazine-induced dyskinesias; however, specific cases of the occurrence of tardive dyskinesia with the use of promethazine hydrochloride have not been reported.

Based on data available to the agency (Ref. 6), FDA finds that promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis. A review of NPA and NDTI data for the period 1975 to 1981-1982 (Ref. 6) shows that the major use of the manufacturer's promethazine hydrochloride as a prescription drug is in combination products for acute cough/cold therapy. Single entity promethazine hydrochloride tablets are most frequently used for antiemetic actions and have the highest percentage of continued use. The data show that virtually all of the manufacturer's promethazine combination drug products are used for "cough/cold" indications while their use as an "antihistamine/anti-allergy" drug is virtually nil. The data also show that the single-ingredient promethazine drug products (i.e., tablets and syrup) are used as an antihistamine/antiallergy drug to a limited degree (i.e., average of 12 percent of the NDTI mentions for the period 1975 to 1981-1982). In addition, the NDTI data indicate that these promethazine products are used mostly on a short-term rather than on a long-term basis, with the exception of single ingredient tablets (Ref. 6). The high ratios of new to refill prescriptions in the NPA data also demonstrate that these products are not used on a long-term basis with the exception of single ingredient tablets (Ref. 6). Long-term use of the single ingredient tablets most frequently represents its use as an antiemetic in chronic illnesses, such as cancer, and not as an antihistamine in patients with allergic rhinitis. The conclusion that promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis is further supported by the manufacturer's statement in its submission that "the average course of therapy under a prescription for an oral promethazine product is about 6-9 days" (Ref. 3).

The agency believes that many consumers who use OTC antihistamines

to treat the symptoms of allergic rhinitis use these products on a long-term basis because the symptoms of allergic rhinitis usually occur for extended periods of time. However, promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis in the OTC target population, i.e., patients with allergic rhinitis. Therefore, there is no assurance that long-term use of promethazine hydrochloride as an OTC antihistamine will not cause the serious side effect tardive dyskinesia.

Accordingly, the agency remains unpersuaded that promethazine, as a phenothiazine, can be generally recognized as safe for OTC use. Many of the comments received in response to the Panel's Category I recommendation for promethazine hydrochloride were from health professionals who opposed OTC status for this drug. The CDB raised the concern in its May 7, 1982 letter that promethazine, as a phenothiazine, is distinct from other antihistamines in terms of its chemical structure and its adverse effects on the central nervous system (Ref. 1). In its petition (Ref. 4), the manufacturer acknowledged that promethazine is chemically related to phenothiazines, but that it is widely recognized that differences in chemical structures and pharmacology substantially lessen the possibility that promethazine could cause the range of side effects associated with other phenothiazines (Ref. 8). The manufacturer also stated that the Panel concluded, after analysis of published reference studies and adverse experience reports on promethazine, that this drug does not cause the wide range of serious or potentially toxic effects that characterize other members of the chemical class of phenothiazines (41 FR 38390). Despite the Panel's recommendation, at this time, FDA is not assured that general recognition of the safety of promethazine hydrochloride for OTC use has been adequately established. The agency is therefore proposing that promethazine hydrochloride as a single ingredient be Category III in this tentative final monograph. The agency specifically invites public comment on the issues discussed above and on the suitability of promethazine hydrochloride for OTC use as a single entity antihistamine drug. Combination drug products containing promethazine hydrochloride will be discussed in the combinations segment of the cough-cold tentative final monograph, in a future issue of the Federal Register.

## References

- (1) Letter from W.E. Gilbertson, FDA, to D.L. Shaw, Wyeth Laboratories, coded LET074, Docket No. 76N-052H, Dockets Management Branch.
- (2) Mendelis, P.S., "Antipsychotic Drugs and Choreaathetosis," Adverse Drug Reaction Highlights, Division of Drug Experience, Center for Drugs and Biologics, FDA, Rockville, MD, January 25, 1982.
- (3) Comment No. C00188, Docket No. 76N-052H, Dockets Management Branch.
- (4) Comment No. CP0002, Docket No. 76N-052H, Dockets Management Branch.
- (5) Letter from W.F. Randolph, FDA, to S.J. Land and W.W. Vodra, Arnold & Porter, coded PAV, Docket No. 76N-052H, Dockets Management Branch.
- (6) Unpublished data obtained from the National Prescription Audit and the National Disease and Therapeutic Index data systems, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (7) Baldessarini, R.J., "Drugs and the Treatment of Psychiatric Disorders," in "The Pharmacologic Basis of Therapeutics," 6th Ed., edited by A.G. Gilman, L.S. Goodman, and A. Gilman, Macmillan Publishing Co., New York, pp. 391-447, 1980.
- (8) Domino, E.F., "Antipsychotics: phenothiazines, Thioxanthenes, Butyrophenones, and Rawolfia Alkaloids," in "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., New York, p. 471, 1971.

## C. Comments on Specific Antihistamine Active Ingredients

10. One comment submitted a study of the effectiveness of phenyltoloxamine citrate to support its reclassification from Category III to Category I as an OTC antihistamine active ingredient (Ref. 1).

The agency has reviewed the study and concludes that this study alone is inadequate to reclassify phenyltoloxamine citrate as a category I antihistamine active ingredient. After a statistical analysis of the data, the agency recognizes that the study demonstrates that there is a statistically significant difference between the pharmacologic action of the placebo and phenyltoloxamine in favor of the active ingredient at 1- and 2-hour intervals after a single dose has been given. However, the study does not demonstrate the effectiveness of phenyltoloxamine over a long enough period of time when given on a dosage schedule that would be representative of the actual conditions under which the drug would be used. The single-dose study can be characterized as a clinical pharmacology study and does not demonstrate that phenyltoloxamine citrate is clinically effective.

Additional data from multiple-dose clinical studies carried out over a period of at least 1 week, and including an adequate number of patients per dose

level as well as placebo, demonstrating the effectiveness of phenyltoloxamine are necessary to reclassify this active ingredient in Category I. There may be a problem of carry-over effect in a crossover study in which each patient is on a drug for a week or more. Therefore, a sufficient washout period should be allowed if a crossover design is used. Phenyltoloxamine citrate will remain in Category III as an OTC antihistamine active ingredient until additional data are received, reviewed, and accepted by the agency.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 2).

## References

- (1) Comment Nos. C00168, LET003, and SUP007, Docket No. 76N-0052, Dockets Management Branch
- (2) Letter from W.E. Gilbertson, FDA, to A.D. Flanagan, Warner/Chilcott, coded C00168/ANS, Docket No. 76N-052H, Dockets Management Branch.

## D. Comments on Dosages for Antihistamine Active Ingredients

11. Several comments disagreed with the Panel's recommendation to increase the currently available OTC dosage of chlorpheniramine maleate from 2 mg every 4 to 6 hours to 4 mg every 4 to 6 hours with a maximum daily dose of 24 mg. The comments stated that chlorpheniramine maleate has been previously available only by prescription at the 4-mg dosage level and that the increase in dosage from 2 to 4 mg will lead to undesirable side effects, especially excessive drowsiness and overdosage. One comment recommended that chlorpheniramine maleate should continue to be sold OTC in its present dosage form. Another comment stated that the data on which the Panel based its decision to increase the maximum daily dose from 16 to 24 mg were inadequate. The comment explained that the majority of patients treated at the 24-mg daily dosage level were reported in a single uncontrolled study and were selected from a population of patients with a long history of allergy. Many patients had previously received antihistamine therapy. The comment questioned whether this group of patients is appropriate to assess the need for the higher OTC dose of chlorpheniramine maleate. The comment recommended that the maximum daily dose of chlorpheniramine maleate for OTC use be 16 mg since there are adequate data to support this dosage.

The agency has reviewed these comments and the data evaluated by the Panel and notes the Panel's conclusion

that chlorpheniramine maleate has not been shown to be effective for adults at a dose less than 4 mg. In addition, chlorpheniramine maleate has been marketed first as a prescription drug product and then as an OTC drug product for many years at the Panel's recommended adult dose of 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. The safety and effectiveness of chlorpheniramine maleate at this dosage have been widely recognized. The agency concludes that chlorpheniramine maleate is safe and effective for OTC use at the Panel's recommended 4-mg dosage level. Therefore, it is unnecessary to change the Panel's recommended dosage in this tentative final monograph by restricting the dosage to 16 mg in 24 hours.

13. One comment expressed concern that certain time-release dosage forms containing chlorpheniramine maleate appear to release all of the ingredient in a short period of time. The comment argued that such dumping causes marked drowsiness in some patients. The comment, however, did not make any specific recommendation to the agency.

Timed-release formulations are considered new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). Timed-release formulations are so complex that the state of the art does not permit standardization to the point of inclusion in an OTC drug monograph as a Category I condition. (See 42 FR 56736.) In order to market these drug products, an approved NDA, containing appropriate bioavailability data, is required under section 505 of the act (21 U.S.C. 355) and FDA regulations at Part 314 (21 CFR 314). This requirement is based on the agency's recognition that there is a possibility of overdosage if products that are designed to release the active ingredients over a prolonged period are improperly manufactured, and the active ingredients are released all at once or over too short a time interval.

Chlorpheniramine maleate is generally recognized as safe at an adult oral dosage of 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. An NDA is required for any timed-release product containing chlorpheniramine maleate.

## E. Comments on Labeling of Antihistamine Drug Product

13. Several comments stressed the importance of making consumers aware through appropriate label warnings that drowsiness is a potential side effect of the use of antihistamines. One comment

specifically recommended that the warning state "Caution: May cause drowsiness. Alcohol may intensify this effect. Use care when operating a car or dangerous machinery."

The agency agrees with the comments that consumers should be warned that drowsiness is a potential side effect of antihistamine active ingredients. In fact, the Panel recommended the warnings "May cause drowsiness" or "May cause marked drowsiness" in § 341.72(b) (6) and (7) of its monograph. The degree and the frequency of the drowsiness produced by a specific antihistamine active ingredient determines which one of the above warnings is required.

The specific warning suggested by one comment would combine the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or dangerous equipment when taking antihistamines. Combining these related warnings would be beneficial to consumers. However, the agency does not believe that all of the specific language suggested by the comment should be used in the warnings. The comment suggests that the warning "Alcohol may intensify this effect" be substituted for the Panel's recommended warning "Avoid alcoholic beverages while taking this product." The agency has determined that the consumer must be warned to avoid alcohol to ensure the safe use of antihistamines on an OTC basis. Moreover, adding the phrase "alcohol may increase the drowsiness effect" to the warning provides more information to the consumer as to why alcohol should be avoided while taking an antihistamine. The agency has, therefore, included this phrase in the warning.

In addition, the agency believes that revising the Panel's recommended wording " \* \* \* operating heavy machinery" to the wording " \* \* \* operating machinery" better conveys the intent of the Panel. Some equipment that requires mental alertness to operate safely is not "heavy." In addition, warning consumers to use care when operating "dangerous" machinery, as the comment suggests, may not be adequate. Consumers may not consider some machinery dangerous when operated by an alert individual. However, virtually all machinery is potentially dangerous if operated by a person who is drowsy and not alert.

The agency concludes that combining the specific labeling suggested by the comment with the warnings recommended by the Panel, with some modifications, will provide more informative labeling for the consumer. Therefore, the warnings concerning

drowsiness, the use of alcohol, and driving a motor vehicle or operating machinery have been revised in this tentative final monograph. Section 341.72(c)(3) reads as follows: "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery." Section 341.72(c)(4) reads as follows: "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

14. One comment suggested that antihistamines should be labeled to inform consumers that these drugs are useful in treating allergic rhinitis and hives, but should not be labeled for treating the symptoms of asthma.

The Panel recommended that antihistamines be labeled for use in treating symptoms of allergic rhinitis. The agency agrees with the comment and the Panel's recommendations regarding this use.

The Panel recommended as part of § 341.72(b)(2), which has been redesignated § 341.72(c)(2) in the tentative final monograph, that antihistamines be labeled with a warning that persons with asthma should not take them except under the advice and supervision of a physician. The Panel pointed out in its report that many physicians consider the drying side effect of antihistamines to be undesirable in patients with bronchial asthma, and some doctors maintain that such drugs should be contraindicated in patients with this disease. The agency concurs with this recommendation and the warning proposed by the Panel.

Hives as a symptom of an allergic reaction was not included in the Panel's report. No data were submitted to the Panel concerning the use of antihistamines for hives, nor were any data reviewed by the Panel concerning this use of antihistamines. The comment also did not provide any data to substantiate its recommendation. Accordingly, an indication for the use of antihistamines in the treatment of hives as a symptom of an allergic reaction is not being proposed in this tentative final monograph.

15. Several comments pointed out that some OTC products containing antihistamines may be labeled and marketed for use only in pediatric populations. The comments argued that certain warnings and caution statements in the Panel's recommended monograph, i.e., "Do not take this product if you have glaucoma or difficulty in urination due to enlargement of the prostate

gland, avoid driving a motor vehicle or operating heavy machinery, and avoid alcoholic beverages while taking this product," apply only to adults and should not be required on products labeled strictly for use in children. The comments recommended that an exempting statement should be added to the monograph under § 341.50(c) stating, "Warnings which are inappropriate for children's products may be eliminated in the labeling of products containing dosage instructions for children only."

The agency agrees that the warnings recommended by the Panel in § 341.72(b)(2), (3), and (4), which have been redesignated as § 341.72(c)(2), (3), and (4) in this tentative final monograph, concerning operating a motor vehicle or machinery, avoiding alcoholic beverages, and the part of the warning statements concerning "difficulty in urination due to enlargement of the prostate gland" are not necessary in the labeling of products intended only for pediatric use. These warnings are not applicable to children and their presence in the labeling would tend to distract parents from label warnings which are important. However, the agency does not agree that the part of the warning about glaucoma in § 341.72(b)(2) should be deleted from the labeling of pediatric products in this tentative final monograph because glaucoma does occur in children (Refs. 1 and 2). In addition, the agency is proposing that the warnings be reworded to reflect the administration of the product by adults rather than self-administration. Accordingly, the tentative final monograph is amended by adding the following to new § 341.72(c):

(6) *For products labeled for children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (g), (h), (i), (j), and (k).* "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride and doxylamine succinate identified in*

§ 341.12(e) and (f). "May cause marked drowsiness."

#### References

- (1) Scheie, H.G., and D.M. Albert, "Textbook of Ophthalmology," 9th Ed., W.B. Saunders Co., Philadelphia, pp. 542-547, 1977.
- (2) Ellis, P.P., and D.L. Smith, "Handbook of Ocular Therapeutics and Pharmacology," 4th Ed., the C.V. Mosby Co., St. Louis, p. 108, 1973.

16. One comment disagreed with the Panel's recommended label warning for pheniramine maleate that states "May cause marked drowsiness." The comment pointed out that pheniramine maleate is in the same chemical class of antihistamines as chlorpheniramine and brompheniramine, i.e., the alkylamines, that this class of antihistamines causes the least amount of drowsiness, and that the Panel recommended the less severe warning "May cause drowsiness" for chlorpheniramine and brompheniramine maleate. The comment urged the agency to require the same label warning, "May cause drowsiness", for pheniramine maleate as allowed for chlorpheniramine and brompheniramine maleate.

The agency has reviewed the data cited in the Panel's report concerning the sedative effects of pheniramine maleate as compared with brompheniramine maleate and chlorpheniramine maleate. In one study reviewed by the Panel, 20 percent of 171 patients receiving a 25-mg dose of pheniramine maleate experienced sedation as a side effect (Ref. 1). In comparison, the Panel states at 41 FR 38382 that brompheniramine maleate produced sedation in 20 percent of less of the individuals taking the ingredient and at 41 FR 38383 that chlorpheniramine maleate produced sedation in 10 to 20 percent of the individuals taking the ingredient. In another study reviewed by the Panel, the frequency of side effects, chiefly drowsiness, seen in 184 subjects receiving 10 mg pheniramine did not exceed the number of side effects in an equal number of subjects receiving a placebo (Ref. 2). Roth and Tabachnick (Ref. 3) have classified the sedative effect of pheniramine maleate as "moderate," compared to a classification of "slight sedation" for brompheniramine maleate and chlorpheniramine maleate. However, Roth and Tabachnick (Ref. 3) did not classify the sedative effect of pheniramine as "marked sedation." The agency agrees with the comment that the warning regarding drowsiness for pheniramine should be the same as that required for chlorpheniramine and brompheniramine. The agency

concludes that the data reviewed by the Panel do not support the need for a stronger warning regarding drowsiness for drug products containing pheniramine maleate. Therefore, the agency proposes to change the warning statement for pheniramine maleate to "May cause drowsiness."

#### References

- (1) Loveless, M.H., and M. Dworin, "Allergy and Antihistamine Therapy: A Review," *The Bulletin of the New York Academy of Medicine*, 25:473-487, 1949.
- (2) Lowell, F.C., et al., "The Antihistamine Drugs in the Treatment of the Common Cold," *New England Journal of Medicine*, 244:132, 1951.
- (3) Roth, F.E., and I.I.A. Tabachnick, "Histamine and Antihistamine," in "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., New York, p. 1009, 1971.

17. One comment stated that the Panel's recommended warning in § 341.72(b)(8), "Caution: May cause nervousness and insomnia in some individuals," is unnecessary for phenindamine tartrate. The comment cited OTC Volume 040126 (Ref. 1) for review with respect to the necessity for the above warning.

The agency has reviewed six references contained in OTC Volume 040126 that were reviewed and cited by the Panel in its report and finds that insomnia and nervousness are dominant side effects which may occur with the use of phenindamine tartrate. Paul et al. (Ref. 2) evaluated phenindamine tartrate in 280 patients. Sleeplessness occurred in 6.4 percent and nervousness in 5.4 percent. In this study, the total daily dosage ranged from 25 to 150 mg, with most adults taking 25 mg three times a day. McGavack et al. (Ref. 3) found that dryness of the mouth, insomnia, and constipation were the major symptoms in patients receiving a total daily dose of 75 to 600 mg of phenindamine tartrate. Boyd, Weissberg, and McGavack (Ref. 4) found that 24 percent of patients who received a total daily dose of 150 mg experienced insomnia and dryness of the mouth. Crip and Aaron (Ref. 5) evaluated 389 patients who received a dosage of 25 mg of phenindamine tartrate every 4 hours and found that 89 (23 percent) experienced side reactions. Of the 89 patients who had side reactions, 22 percent experienced nervousness and palpitations, 22 percent had nausea, and 10 percent had insomnia.

Pennypacker and Sharpless (Ref. 6) gave patients 25 to 50 mg of phenindamine tartrate daily and found that of 40 patients, 35 percent (14) experienced insomnia and 22.5 percent (9) tenseness. Cohen, Davis, and Mowry

(Ref. 7) studied 292 patients who received a total daily dose of 50 to 200 mg of phenindamine tartrate; 54 of the patients (18 percent) experienced side effects. Of these 54 patients, 33 experienced nervous side reactions.

In other unpublished studies contained in OTC Volume 040126, the recommended effective adult oral dosage of 25 mg of phenindamine tartrate was not used. The evaluations were done with tablets which contained only 10 mg of phenindamine tartrate. For this reason, the data on side effects reported in these studies cannot be used to support the comment's request to eliminate the warning.

Because the data reviewed by the Panel (Refs. 1 through 7) show that phenindamine tartrate may cause insomnia and nervousness, the agency agrees with the Panel's recommendation that the warning, "May cause nervousness and insomnia in some individuals," be required for phenindamine tartrate.

#### References

- (1) OTC Volume 040126.
- (2) Paul, A.B., et al., Clinical Evaluation of a New Antihistaminic Compound," *The Laryngoscope*, 58:1044-1054, 1948.
- (3) McGavack, T.H., et al., "Clinical Evaluation of Phenindamine (2-Methyl-9-phenyl-2, 3, 4, 9-Tetra-hydro-1-Pyridindene Hydrogen Tartrate) as an Antihistamine Agent," *American Journal of the Medical Sciences*, 216:437-475, 1948.
- (4) Boyd, L.J., J. Weissberg, and T.H. McGavack, "Tolerance Studies of the Antihistamine Drug Thephorin," *New York State Journal of Medicine*, 48:1596-1598, 1948.
- (5) Crip, L.H., and T.H. Aaron, "Thephorin: An Experimental and Clinical Evaluation in Allergic States," *Journal of Allergy*, 19:304-312, 1948.
- (6) Pennypacker, C.S., and I. Sharpless, "Clinical Study of a New Antihistaminic Drug—Thephorin," *Pennsylvania Medical Journal*, 51:1407-1411, 1948.
- (7) Cohen, E.B., H.P. Davis, and W.A. Mowry, "Thephorin in Allergy," *American Journal of Medicine*, 5:44-47, 1948.

18. One comment stated that the Panel used an inappropriate standard in categorizing some Category II claims and that the claims "fast" and "prompt" were rejected by the Panel for antihistamine labeling because the time is indeterminate. The comment stated that if the drug provides fast or prompt relief, as these terms are understood by consumers, then these claims are not misleading and should be permitted.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients

and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: products statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

As with all OTC drug products, antihistamines are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which antihistamines achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast" or "prompt" are outside the scope of the OTC drug review. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the monograph.

The agency emphasize that even though terms such as "fast" or "prompt" are outside the scope of the OTC drug review for this class of products, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

Moreover, any statement or term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the Scope of the monograph may be included elsewhere in the labeling, provided the are not false or misleading.

#### F. Comments on Testing Guidelines

19. Two comments disagreed with the Panel's recommended Category III testing criteria for the evaluation of antihistamines in treating the symptoms of the common cold. (See part VII, paragraph C.2.d. of the Panel's report—Methods of study (41 FR 38396).) The comments argued that it was unreasonable to give the antihistamine throughout the entire course of the cold if the specific symptom being treated, e.g., runny nose, is no longer in

evidence. The comments recommended that the testing criteria be changed so that the study need only be of sufficient length to distinguish clearly between the effect of the drug and the placebo. One of the comments argued that requiring three positive studies from three different investigators, as the Panel recommended, was unnecessary and contended that because two studies were considered adequate in other Category III testing recommended by the Panel, the same requirement should apply in this case.

The other comment argued that the criteria for stratifying patients according to age, sex, and severity of symptoms were unnecessary. The comment contended that stratifying by sex and age would be insignificant as a factor in patients' response to medication and that in view of other strict criteria, which would eliminate potential patients, stratifying by sex and age would result in an additional loss of qualified patients for investigation. The comment believe that stratifying by symptom severity would be too prone to subject interpretation because one could not specify when peak severity would occur in the course of the illness. Both comments recommended that the agency reject the specified panel testing criteria.

The agency has reviewed data in studies designed to demonstrate the effectiveness of the antihistamine chlorpheniramine maleate in treating the symptoms of the common cold that were submitted in response to the advance notice of proposed rulemaking (Ref. 1). Although they do not meet all of the criteria of the Panel's testing guidelines, they have been accepted by the agency as demonstrating the effectiveness of chlorpheniramine for use in treating the symptoms of runny nose and sneezing when associated with the common cold. (See comment 4 above.) One of the acceptable studies did not follow the patients for the entire course of the illness. The study covered the time period over which the symptoms studied were in evidence. Therefore, studies which are of sufficient length to distinguish between the effectiveness of the drug and the placebo in treating a particular symptom are acceptable. In addition, because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine maleate allow Category I status for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients. (See comment 4 above.)

In summary, the agency concludes that adequate data demonstrating the safety and/or effectiveness of a Category III condition are necessary to reclassify that condition to Category I status but that this does not necessarily require that the guidelines recommended by the Panel be followed. The Panel's testing criteria are considered to be recommendations to the agency. Although the submitted chlorpheniramine studies did not stratify patients according to age, sex, severity, and duration of illness, they have been accepted by the agency. Stratification of patients by the above criteria is not a necessary requirement for studies designed to demonstrate the effectiveness of antihistamines in treating symptoms associated with the common cold. Studies submitted in support of the effectiveness and safety of a Category III condition are evaluated on the basis of their own merits rather than on how well they meet the Panel's requirements. However, the agency emphasizes that each study submitted to support a request for the reclassification of a Category III condition to Category I status must substantiate the reclassification whether or not the Panel's recommended guidelines are followed.

#### Reference

(1) Comment Nos. SUP004 and SUP005, Docket No. 76N-0052, Dockets Management Branch.

#### II. The Agency's Tentative Adoption of the Panel's Report

##### A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made some changes in the categorization of antihistamine active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of antihistamine active ingredients recommended by the Panel and the proposed categorization by the agency.

Antihistamine active ingredients	Panel	Agency
Brompheniramine maleate .....	I	I
Chlorpheniramine maleate .....	I	I
Dexbrompheniramine maleate .....	(1)	I
Dexchlorpheniramine maleate .....	(1)	I
Diphenhydramine hydrochloride .....	I	I
Methapyriene fumarate .....	I	II
Methapyriene hydrochloride .....	I	II
Phenindamine tartrate .....	I	I
Phenindamine tartrate .....	I	I

Antihistamine active ingredients	Panel	Agency
Phenyltoloxamine citrate	III	III
Phromethazine hydrochloride	I	III
Pyrimamine maleate	I	I
Theridilamine hydrochloride	III	III
Thonzylamine hydrochloride	I	I
Triprolidine hydrochloride	(1)	I

<sup>1</sup> Not reviewed.

The agency points out that any of the antihistamines proposed as Category I in this tentative final monograph, except dexchlorpheniramine (see comment 7 above), may be marketed OTC in a combination drug product in accord with the Panel's permitted combinations of Category I active ingredients in the analgesic, antitussive, and decongestant categories recommend in § 341.40 of the advance notice of proposed rulemaking (41 FR 38420). The tentative final monograph on cough-cold combination drug products will be published in a future issue of the Federal Register and will discuss the combinations proposed by the agency. Any interim marketing that is permitted is subject to the agency's conclusions in the final monograph.

**2. Testing of Category II and Category III conditions.** The Panel recommended testing guidelines for antihistamine drug products (41 FR 38329 and 38394). The agency's position regarding the Panel's testing guidelines is discussed in comment 23 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any antihistamine ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

#### *B. Summary of the Agency's Changes in the Panel's Recommendations*

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the antihistamine section of the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency has modified § 341.3(d) and § 341.72(a) (redesignated § 341.72(b) in the tentative final monograph) to include the use of antihistamines for the

temporary relief of runny nose and sneezing associated with the common cold. The agency has reviewed and accepted data which demonstrate the effectiveness of chlorpheniramine maleate in treating these symptoms when associated with the common cold. In addition, because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted on chlorpheniramine allow an indication for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients. The agency proposes to substitute the term "runny" for the term "running" which was used by the Panel. The agency recognizes that the term "runny" is grammatically correct, particularly when it is used in reference to a condition of the nose. The agency believes the term "runny" is more commonly used than the term "running" and is, therefore, better understood by consumers. (See comment 4 above.)

2. Dexbrompheniramine maleate has been marketed as a single ingredient prescription drug product under an approved NDA for 23 years (Ref. 1). It has also been marketed in combination with pseudoephedrine sulfate under an approved NDA for 19 years as a prescription drug product that delivers an adult dose of 2 mg of dexbrompheniramine every 4 hours using a sustained release delivery from a 6-mg tablet taken every 12 hours (Ref. 2). This product has been approved for OTC marketing under an NDA (Ref. 3). The agency has reviewed the literature concerning the safety and effectiveness of dexbrompheniramine maleate as an antihistamine. Based on this literature, and the review by the Drug Efficacy Study Group (DESI) published in the Federal Register of March 19, 1973 (38 FR 7265), the agency believes that the drug can be generally recognized as safe and effective for OTC use.

Dexbrompheniramine maleate is the dextrorotatory isomer (d-isomer) of brompheniramine maleate, which is a racemic histamine antagonist composed of d- and l-isomers. Pharmacological studies have shown that the antihistaminic activity resides almost exclusively in the d-isomer, and that there is very little difference in the toxicities of the d-isomer and the d,l mixture in experimental animals (Ref. 4). Because dexbrompheniramine maleate is about twice as potent as brompheniramine maleate, it is used in clinical practice at one-half the dose of brompheniramine maleate.

The agency has reviewed studies by Frank (Ref. 5), Olansky and Olansky (Ref. 6), and Romanoff and Guidatti (Ref. 7) concerning the safety and effectiveness of dexbrompheniramine maleate alone. The studies showed the drug to be an effective antihistamine, at a dosage of 2 mg, with a low incidence of side effects (drowsiness, slight dizziness). One of the studies, using a double-blind design, showed a significant response to dexbrompheniramine, compared to a placebo, among patients with respiratory symptoms due to allergic rhinitis and pollinosis. Symptoms such as itching, sneezing, and watery eyes were relieved in the patients receiving the drug (Ref. 7).

In addition, the agency has reviewed studies by Mayer and Savitt (Ref. 8), Kapstad and Warland (Ref. 9), Lofkvist and Svenson (Ref. 10), and Fierburg (Ref. 11) concerning the safety and effectiveness of dexbrompheniramine maleate in combination with pseudoephedrine sulfate. All of these studies were double-blinded and evaluated combination drug products that are marketed under the approved NDA (Refs. 8 through 11). The studies were performed in patients with perennial allergic rhinitis or vasomotor rhinitis. A crossover design was used in three of the studies (Refs. 8, 10 and 11). All of these studies demonstrated that dexbrompheniramine maleate in combination with pseudoephedrine sulfate is effective in relieving symptoms when compared to several different reference drugs or placebos. Patients receiving the dexbrompheniramine-pseudoephedrine combination experienced a lessening of sinus congestion and of runny nose. Three other studies, which were not double-blind but controlled clinical comparisons, showed similar results (Refs. 12, 13, and 14).

Side effects reported in these studies were similar to those reported for other antihistamine-nasal decongestant drugs and included drowsiness, dry mouth and dry throat, dizziness, nausea, swelling in the face, headache, restlessness, tachycardia, and constipation. There were relatively few side-effects reported in all, and in only one case did a patient reduce the medication to one tablet a day because of drowsiness and dry mouth (Ref. 5).

A review of FDA adverse reaction reports since 1970 indicates that conditions such as rash, hypertension, transient myopia, nervousness, and insomnia have been reported in cases where the combination drug dexbrompheniramine-pseudoephedrine

was taken (Ref. 15). In these cases, overdose was not indicated, nor was enough information available to indicate a possible cause-and-effect relationship between the use of dexbrompheniramine maleate and the reaction.

Based on the above data and information, the agency believes that dexbrompheniramine maleate can be generally recognized as safe and effective for OTC use. The agency is therefore proposing that dexbrompheniramine maleate be classified as Category I as an OTC antihistamine at a dose of 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, for adults and a dose of 1 mg every 4 to 6 hours, not to exceed 6 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes a dose of 0.5 mg every 4 to 6 hours, not to exceed 3 mg in 24 hours, for children 2 to under 6 years of age under professional labeling in the tentative final monograph. The labeling warnings are identical to those being proposed for brompheniramine maleate.

Dexbrompheniramine maleate was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has approved an NDA that currently allows the OTC marketing of products containing dexbrompheniramine. Thus, FDA does not believe it is necessary to prohibit OTC marketing of dexbrompheniramine under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this tentative final monograph and subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

#### References

- (1) Letter from I. Siegel, FDA, to White Laboratories, Inc., OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Letter from J.W. Winkler, FDA, to White Laboratories, Inc., OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (3) Letter from J.P. Mann, FDA, to Schering Corporation, OTC Volume 04HTFM, Docket No. 76N-052H, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (4) Roth, F.E., "Antihistamine Activity of the Optical Isomers of Pheniramine and its Chlor- and Brom-Substituted Derivatives," *Chemotherapy*, 3:120-127, 1961.
- (5) Frank, D.I., "Clinical Evaluation of Dexbrompheniramine Maleate (Disomer) in Ear, Nose and Throat Allergies," *Current Therapeutic Research*, 1:115-121, 1959.

- (6) Olansky, M., and S. Olansky, "Antihistaminic Activity of Dexbrompheniramine (Disomer). Appraisal in Pediatric Allergies," *Annals of Allergy*, 18:415-419, 1960.
  - (7) Romanoff, A., and F.P. Guidotti, "Evaluation of Dexbrompheniramine Maleate in Allergy by Double-Blind Procedure. Preliminary Report," *New York State Journal of Medicine*, 60:3800-3803, 1960.
  - (8) Mayer, P.S., and A.E. Savitt, "Allergic Rhinitis and Air Pollution: A Double-Blind Crossover Analysis," *The Eye, Ear, Nose and Throat Monthly*, 51:9-12, 1972.
  - (9) Kapstad, B., and A. Warland, "Therapeutic Effectiveness of an Oral Anti-Histamine Combination (Dexbrompheniramine Maleate/D-Isoephedrine Sulfate) in the Treatment of Patients with Allergic Rhinitis," *Acta Allergologica*, 31:233-226, 1976.
  - (10) Lofkvist, T., and G. Svensson, "A Comparative Evaluation of Oral Decongestants in the Treatment of Vasomotor Rhinitis," *The Journal of International Medical Research*, 6:56-60, 1978.
  - (11) Fierberg, A.A., "Allergic Nasal Congestion. Effects of Oral Treatment with a Combination of Dexbrompheniramine and D-Isoephedrine," *Annals of Allergy*, 22:324-328, 1964.
  - (12) Frank, D.I., "Evaluation of Two Sustained-Action Oral Decongestants: A Controlled Study," *Current Therapeutic Research*, 6:158-161, 1964.
  - (13) Pullen, F.W., and W.W. Montgomery, "Comparative Evaluation of Oral Decongestants," *Archives of Otolaryngology*, 77:10-12, 1963.
  - (14) Jungert, S., "A Comparison of the Efficacy and Safety of Two Preparations in the Treatment of Allergic and Vasomotor Rhinitis, Disophril Chronosule Capsules and Tavegil Tablets," *Current Therapeutic Research*, 24:269-273, 1978.
  - (15) Department of Health and Human Services, Food and Drug Administration, Adverse Reaction Summary Listings, pertinent pages for 1970-82, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
3. The agency has proposed placing dexchlorpheniramine maleate in Category I based on the safe and effective use of this drug product as a prescription drug under an approved ANDA, a review of FDA adverse reaction reports, and the safe and effective use of the racemic mixture, chlorpheniramine maleate, as an OTC drug product for many years. However, it may not be marketed OTC at this time. (See comment 7 above.)
4. The agency has deleted the reference to methapyrilene in § 341.12(e), the reference to § 341.12(e) in § 341.72(b)(7), and the reference to methapyrilene in § 341.90(f) of the Panel's recommended monograph. These sections provided dosages, a warning, and professional labeling for methapyrilene preparations, which are

no longer marketed because of the NCI study showing that these drugs are associated with the development of tumors in laboratory animals. The agency has reclassified methapyrilene preparations in Category II. (See comments 1 and 6 above.)

5. The agency has deleted the reference to promethazine hydrochloride in § 341.12(h), the reference to § 341.12(h) in § 341.72(b)(7), and the reference to promethazine hydrochloride in § 341.90(i) of the Panel's recommended monograph. These sections provided dosages, a warning, and professional labeling for promethazine hydrochloride. In the agency's preamble to the Panel's report and recommended monograph (41 FR 38312), the agency disagreed with the Panel's Category I classification of promethazine hydrochloride. The agency concludes that general recognition of the safety of this ingredient for OTC use has not been adequately established. Consequently, the agency has reclassified promethazine hydrochloride in Category III. (See comment 9 above.)

6. Triprolidine hydrochloride has been marketed under an approved NDA for 24 years as a prescription drug product at a dose of 2.5 mg every 6 to 8 hours for adults, a dose of 1.25 mg every 6 to 8 hours for children 6 to 12 years of age, a dose of 0.938 mg every 6 to 8 hours for children 4 to under 6 years of age, a dose of 0.625 mg every 6 to 8 hours for children 2 to under 4 years of age, and a dose of 0.313 mg every 6 to 8 hours for infants 4 months to under 2 years of age (Refs. 1 and 2). In addition, drug products containing triprolidine hydrochloride as a single ingredient and in combination with pseudoephedrine hydrochloride have been approved for OTC marketing under NDAs (Ref. 3). In a 1973 Drug Efficacy Study Implementation (DESI) notice (36 FR 9339), the agency concluded that this drug is effective. FDA has reviewed the literature and marketing history of triprolidine hydrochloride as an antihistamine and believes that this drug can be generally recognized as safe and effective for OTC use.

Studies by Fruchard and Fruchard (Ref. 4); Britton et al. (Ref. 5); Wolf fromm and Liacopoulos (Ref. 6); Bye et al. (Ref. 7); Nicholson (Ref. 8); Bye et al. (Ref. 9); and Peck, Fowle, and Bye (Ref. 10) were reviewed for the safety and effectiveness of triprolidine hydrochloride. Most of the studies were double-blind (Refs. 5, 7, 8, and 9). In 27 out of 36 vasomotor rhinitis cases, triprolidine hydrochloride promptly relieved the symptoms (within 15

minutes), had a long duration of action (about 5 to 6 hours), and was well tolerated (Ref. 6). In another study (Ref. 4), good results were reported in all patients with symptoms of spasmodic rhinitis. These authors also reported that triprolidine hydrochloride acts rapidly and is well tolerated. Both studies (Refs. 4 and 6) indicated that triprolidine is a powerful antihistamine and antianaphylactic agent with mild side effects and rapid action. Studies by Nicholson (Ref. 8) and Peck, Fowle, and Bye (Ref. 10) showed that the effect of triprolidine hydrochloride was immediate and lasts for about 7 hours with a maximum effect at the third hour. The double-blind studies of this drug indicated that, after repeated doses of the drug in a 24-hour period, the degree of drowsiness tended to decrease (Refs. 5, 7, and 9). No evidence of an increased drug effect due to accumulation was reported (Ref. 9). The reported side effects were drowsiness (Refs. 4, 5, 6, 7, and 9) and digestive disturbance (Refs. 4 and 6). FDA adverse reaction reports for triprolidine hydrochloride since 1969 show only two reports of rash (Ref. 11).

Based on the above data and information, the agency is proposing that triprolidine hydrochloride be classified as Category I as an OTC antihistamine at a dose of 2.5 mg every 6 to 8 hours, not to exceed 10 mg in 24 hours, for adults, and a dose of 1.25 mg every 6 to 8 hours, not to exceed 5 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes to place in professional labeling a dose of 0.938 mg every 6 to 8 hours, not to exceed 3.75 mg in 24 hours, for children 4 to under 6 years of age; a dose of 0.625 mg every 6 to 8 hours, not to exceed 2.5 mg in 24 hours, for children 2 to under 4 years of age; and a dose of 0.313 mg every 6 to 8 hours, not to exceed 1.25 mg in 24 hours, for infants 4 months to under 2 years of age. The agency is proposing that the general labeling recommended by the Panel for OTC antihistamine drugs be used for triprolidine hydrochloride.

Triprolidine was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has approved several NDAs that currently allow the OTC marketing of products containing triprolidine. Thus, FDA does not believe it is necessary to prohibit OTC marketing of triprolidine under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this tentative final monograph and

subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

#### References

- (1) Letters from P. DeFelice, FDA, to Burroughs-Wellcome Co., Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
  - (2) Copies of FDA-approved labeling from NDA 11-110 and NDA 11-496, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
  - (3) Letters from J.P. Mann, FDA, to Burroughs-Wellcome Co., OTC Volume 04HTFM, Docket No. 76N-052H, Docket Management Branch.
  - (4) Fruchard, J., and J. Fruchard, "Un Nouvel Antihistaminique: Actidil," *Journal de Medecine de Bordeaux et du Sud-Ouest*, 134:1356-1358, 1957.
  - (5) Britton, M.G., et al., "Two Doses of Triprolidine for Treatment of Allergic Rhinitis," *Annals of Allergy*, 4(5):330-332, 1979.
  - (6) Wolfromm, R., and P. Liacopoulos, "Clinical Trial of a New Synthetic Antihistamine-Trans-1 (4 methylephenyl)-1-(2-pyridyl)-3-pyrrolidinoprop-ene Hydrochloride," Extract from *La Semaine des Hopitaux de Paris (La Semaine Medicale Professionnelle et Medico-Sociale)* 13, 1957.
  - (7) Bye, C., et al., "The Effects of Repeated Doses of Triprolidine on Subjective Drowsiness and Performance Tests in Man," *British Journal of Clinical Pharmacology*, 2(4):379p-380p, 1975.
  - (8) Nicholson, A.N., "Effect of the Antihistamines Brompheniramine Maleate and Triprolidine Hydrochloride on Performance in Man," *British Journal of Clinical Pharmacology*, 8:321-324, 1979.
  - (9) Bye, C.E., et al., "Evidence for Tolerance to the Central Nervous Effects of the Histamine Antagonist, Triprolidine, in Man," *European Journal of Clinical Pharmacology*, 12:181-186, 1977.
  - (10) Peck W., A. S. E. Fowle, and C. Bye, "A comparison of triprolidine and Clemastine on Histamine Antagonism and Performance Tests in Man: Implications for the Mechanism of Drug Induced Drowsiness," *European Journal of Clinical Pharmacology*, 8:455-463, 1975.
  - (11) Department of health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969-1982, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
7. The agency has added to § 341.72 a "Statement of identity" paragraph (designated as § 341.72(a)) and a "Directions" paragraph (designated as § 341.72(d)) to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. Inclusion of the "Statement of identity" paragraph has necessitated a redesignation of § 341.72(a) to § 341.72(b), and § 341.72(b) to § 341.72(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the

monograph in Subpart C.

8. The agency has proposed a new indication for the use of antihistamines for the temporary relief of runny nose and sneezing associated with the common cold in paragraph (2) of new § 341.72(b). (See comment 4 and part II, paragraph B. 1. above.) The agency has also combined several required indications under new § 341.72(b)(1). The agency has replaced the Panel's wording "Alleviates, decreases, or temporarily relieves" with the option to select the word "relieves," "alleviates," "decreases," "reduces," or "dries" for the symptom "runny nose" and the option to select the word "relieves," "alleviates," "decreases," or "reduces" for the Symptoms "Sneezing, itching of the nose or throat, and itchy, watery eyes" in the combined indications for antihistamines. These options provide manufacturers the flexibility to select different terms for labeling. Manufacturers are encouraged to submit additional words for possible inclusion as selection options in the "Indications" section of the final monograph for antihistamines drug products. Therefore, indications in § 341.72(a), which has been redesignated § 341.72(b) have been revised as follows: Paragraphs (2), (3), (4), (5), and (6), of § 341.72(a) have been revised and combined in paragraph (1) of new § 341.72(b). The new indication for the use of antihistamines for symptoms associated with the common cold has been added in paragraph (2) of new § 341.72(b). New § 341.72(b) (1) and (2) reflect the combining of indications for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to allergic rhinitis and for the temporary relief of runny nose and sneezing associated with the common cold.

9. The agency has deleted § 341.72(b)(5) of the Panel's recommended monograph. This section provided the warning "Do not give this product to children under 6 years except under advice and supervision of a physician," for all antihistamine drug products. The directions provided under new § 341.72(d) state clearly that a doctor should be consulted for the use of antihistamine drug products in children under 6 years of age. The agency believes that the warning is therefore repetitious and unnecessary.

10. In § 341.72(b) (3), (4), and (8) the Panel recommended the use of the signal word "Caution" in a section of the labeling where the heading "Warnings" is also recommended. The agency notes that historically there has not been a consistent usage for the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and

369.21 (21 CFR 396.20 and 396.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Accordingly, the signal word "Caution" has been deleted from this tentative final monograph.

11. The agency has added to § 341.72(b) (redesignated as § 341.72(c)) a paragraph on warnings that are appropriate for products that are labeled for children under 12 years of age. The agency acknowledges that some warnings which the Panel recommended for all antihistamine drug products are inappropriate for products which are labeled for children under 12 years of age. In addition, the warnings for products labeled for children under 12 years of age have been worded to reflect the administration of the product by adults rather than self-administration. (See comment 15 above.)

12. The agency has combined several warnings under new § 341.72(c) and believes that combining the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or machinery while taking antihistamines will provide more informative labeling for the consumer. Therefore, the warnings (in § 341.72(b), which has been redesignated § 341.72(c)), have been revised as follows: Paragraphs (6), (7), and (8) have been redesignated as (3), (4), and (5). Paragraphs (3) and (4) of § 341.72(b) have been revised, combined, and added to paragraphs (3) and (4) of new § 341.72(c). New § 341.72(c) (3) and (4) reflect a combining of warnings concerning drowsiness and the use of alcohol or operating a motor vehicle or machinery while taking antihistamines. (See comment 13 above.)

13. Because antihistamines have an anticholinergic effect which can reduce the volume of bronchial secretions and cause thickening of these secretions, the Panel recommended that antihistamines

bear a warning that people with asthma not take these drugs unless directed by a doctor, and the agency is proposing such a warning in this tentative final monograph. The agency believes that in addition to this warning, the labeling of antihistamine drug products should include a warning against use of antihistamines in patients with any obstructive pulmonary disease in which clearance of secretions is a problem. The Panel stated that it is important to avoid anticholinergics in the presence of bronchial asthma or chronic obstructive pulmonary disease because of the possibility that anticholinergics may cause secretions to become less fluid and difficult to remove, and thus cause obstruction of the respiratory passages (41 FR 38377). The Panel's recommended warning in § 341.72(b)(2) of the advance notice of proposed rulemaking included asthma, but did not include chronic obstructive pulmonary disease as a contraindication for the use of antihistamines. The agency believes that this warning should be expanded to include all types of chronic obstructive pulmonary disease. This term applies to patients with clinically significant, irreversible, generalized airways obstruction associated with varying degrees of chronic bronchitis, abnormalities in small airways, and/or emphysema (Ref. 1).<sup>1</sup> Because respiratory distress symptoms such as difficulty in breathing and shortness of breath are characteristic of chronic obstructive pulmonary disease, the agency believes that such descriptive terms should also be included in the warning in order to provide more information to the consumer. Therefore, the agency is proposing to amend the Panel's recommended warning to read, "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." The agency is proposing the term chronic pulmonary disease rather than chronic obstructive pulmonary disease in this warning because it believes that the shorter term will be more understandable to consumers.

#### Reference

(1) Berkow, R., editor, "The Merck Manual," 14th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, NJ, pp. 628-635, 1982.

14. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more

commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency proposes to revoke the existing warning and caution statements in §§ 369.20 and 369.21, and exemptions for certain drugs limited by NDAs to prescription sale in § 310.201(a)(13), for oral antihistamine drug products at the time that this monograph becomes effective. The agency proposes to revoke § 310.201(a)(4) and to delete phenyltoloxamine citrate from bearing the warning and caution statements required by § 369.21 at the time that this monograph becomes effective if this ingredient is reclassified in Category I as an OTC antihistamine in the final monograph.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register on February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC antihistamine drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Public Law 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC antihistamine drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antihistamine drug products. Types of impact may include,

but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC antihistamine drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on antihistamine drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, contained in an environmental assessment (under 21 CFR 25.31, proposed in the Federal Register of December 11, 1979; 44 FR 71742), which may be seen in the Dockets Management Branch, Food and Drug Administration.

#### List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics, Expectorants, Bronchodilators, Antitussives, Nasal decongestants, Antihistamines.

On July 9, 1982 at 47 FR 40002, FDA proposed to amend 21 CFR Subchapter D by adding a new Part 341. Proposed Part 341, as amended on October 26, 1982 (47 FR 47520) and October 19, 1983 (48 FR 48576) would be further amended as follows:

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended [5 U.S.C. 553, 554, 702, 703, 704]), and under 21 CFR 5.11, it is proposed to make the following amendments:

#### PART 341—[AMENDED]

1. In proposed Subpart A, § 341.3 is amended by adding new paragraph (d) to read as follows:

#### § 341.3 Definitions.

(d) *Antihistamine drug*. A drug used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold.

2. In proposed Subpart B, new § 341.12 is added to read as follows:

#### § 341.12 Antihistamine active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

- (a) Brompheniramine maleate.
- (b) Chlorpheniramine maleate.
- (c) Dexbrompheniramine maleate.
- (d) Dexchlorpheniramine maleate.
- (e) Diphenhydramine hydrochloride.
- (f) Phenindamine tartrate.
- (g) Pheniramine maleate.
- (h) Pyrilamine maleate.
- (i) Thonzylamine hydrochloride.
- (j) Triprolidine hydrochloride.

3. In proposed Subpart C, new § 341.72 is added and § 341.90 is amended by adding new paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k) to read as follows:

#### § 341.72 Labeling of antihistamine drug products.

(a) *Statement of identity*. The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antihistamine."

(b) *Indications*. The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to both of the following phrases: (1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

(2) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing associated with the common cold."

(c) *Warnings*. The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "May cause excitability especially in children."

(2) "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of

breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(3) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12 (a), (b), (c), (d), (f), (g), (h), (i), and (j)*. "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

(4) *For products containing diphenhydramine hydrochloride identified in § 341.12(e)*. "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

(5) *For products containing phenindamine tartrate identified in § 341.12(f)*. "May cause nervousness and insomnia in some individuals."

(6) *For products that are labeled only for use by children under 12 years of age*. The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (f), (g), (h), (i), and (j)*. "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride identified in § 341.12(e)*. "May cause marked drowsiness."

(d) *Directions*. The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing brompheniramine maleate identified in § 341.12(a)*. Adults: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as

directed by a doctor. Children under 6 years of age: consult a doctor.

(2) *For products containing chlorpheniramine maleate identified in § 341.12(b).* Adults: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(3) *For products containing dexbrompheniramine maleate identified in § 341.12(c).* Adults: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) *For products containing dexchlorpheniramine maleate identified in § 341.12(c).* Adults: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) *For products containing diphenhydramine hydrochloride identified in § 341.12(e).* Adults: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) *For products containing phenindamine tartrate identified in § 341.12(f).* Adults: oral dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) *For products containing pheniramine maleate identified in § 341.12(g).* Adults: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) *For products containing pyrilamine maleate identified in § 341.12(h).* Adults: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(9) *For products containing thonzylamine hydrochloride identified in § 341.12(i).* Adults: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) *For products containing triprolidine hydrochloride identified in § 341.12(j).* Adults: oral dosage is 2.5 to 6 milligrams every 8 to 8 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 6 to 8 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor. (e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

#### § 341.90 Professional labeling.

(b) *For products containing brompheniramine maleate identified in § 341.12(a).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(c) *For products containing chlorpheniramine maleate identified in § 341.12(b).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(d) *For products containing dexbrompheniramine maleate identified in § 341.12(c).* Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(e) *For products containing dexchlorpheniramine maleate identified in § 341.12(d).* Children 2 to under 6 years: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(f) *For products containing diphenhydramine hydrochloride identified in § 341.12(e).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours.

(g) *For products containing phenindamine tartrate identified in § 341.12(f).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(h) *For products containing pheniramine maleate identified in § 341.12(g).* Children 2 to under 6 years of age: oral dose is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(i) *For products containing pyrilamine maleate identified in § 341.12(h).* Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 50 milligrams in 24 hours.

(j) *For products containing thonzylamine hydrochloride identified in § 341.12(i).* Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(k) *For products containing triprolidine hydrochloride identified in § 341.12(j).* Children 2 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 6 to 8 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 6 to 8 hours, not to exceed 1.252 milligrams in 24 hours.

Interested persons may, on or before May 15, 1985 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through

Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data

and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986.

Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

*Commissioner of Food and Drugs.*

Margaret M. Heckler,

*Secretary of Health and Human Services.*

[FR Doc. 85-680 Filed 1-14-85; 8:45 am]

BILLING CODE 4160-01-M